Jumpstarting Research into Neglected Diseases

Unwilling to wait and hope for a cure, patients suffering from rare or little-studied diseases and their families are galvanizing research efforts and driving innovative approaches to develop new treatments.

A decade ago, researchers knew that children with the rare fatal disorder Hutchinson-Gilford progeria syndrome (HGPS) appear to age a lifetime in just a few years, but they had no idea why. "There was no way to think about HGPS in molecular terms," says Susan Michaelis of Johns Hopkins University School of Medicine in Baltimore, Maryland. Today, researchers have not only identified the genetic defect that causes HGPS (a mutation in the gene encoding the nuclear membrane structural protein lamin A) but also are discussing a possible treatment using farnesyl transferase inhibitors (FTIs), a class of anticancer drug. Clinical trials of FTIs could begin within a year.

Michaelis, who coauthored some of the FTI studies, says that one person—Leslie Gordon—deserves credit for touching off this scientific boom. After her 22-month-old son was diagnosed with HGPS in 1998, Gordon helped to launch the Progeria Research Foundation (PRF) in an effort to energize research into the disease. Since then, the organization has doled out 19 research grants, staged the first scientific workshops on HGPS, and gathered tissue from progeria patients and family members. The PRF is now trying to raise $2 million (about four times its annual budget) to bankroll a clinical trial to test the FTIs. An M.D-Ph.D. who had planned to specialize in pediatric ophthalmology, Gordon says that she didn't want to take on the huge task of creating a foundation, but the dearth of resources for researchers and for HGPS families made it necessary. "We had no choice. There was nothing out there."

Gordon is not alone. Advocacy groups started by patients and their relatives are propelling research on an assortment of illnesses. They have taken aim at rare killers such as HGPS, which affects only about 40 children worldwide, and more common diseases that they contend have gotten short shrift from scientists and pharmaceutical companies, including epilepsy and autism.

Patient-oriented groups date to the 1950s, says physician and historian Barron Lerner of Columbia University in New York City. But the aggressive activism of the 1970s and 1980s has colored the attitudes of today's participants, who "won't wait for science to get around to their disease," he says. That impatience shows in tactics that go beyond funneling money into research. Advocacy groups have taken over some of the scientific work themselves, underwriting clinical trials, founding tissue banks, and in at least one case, opening a drug-testing laboratory.

Sowing Scientific Seeds

These organizations play a crucial role by funding risky research that the NIH is reluctant to support, says Nancy Wexler of Columbia University in New York City. A veteran of science and activism, Wexler serves as president of the Hereditary Disease Foundation, which her father established in 1968, and was on the team that tracked down the Huntington's disease gene in 1992. Advocacy groups, she notes, are "usually the only groups to fund research with pilot data."

Such support can be doubly effective. It can enable researchers to amass the data necessary to gain NIH funding. Furthermore, a fresh source of money may entice seasoned scientists and young researchers into working on a neglected disease. According to Dan Geschwind of the University of California, Los Angeles, one organization that has excelled at luring talented scientists is the Cure Autism Now (CAN) Foundation, launched 11 years ago by several families with autistic children. Former head of CAN's scientific steering committee, Geschwind credits the Los Angeles-based organization with attracting "hundreds" of scientists to the field. He is one of the recruits, garnering CAN funds for his efforts to pinpoint autism susceptibility genes. "It's hard to overemphasize the effect of CAN on raising awareness and bringing neuroscientists into research" on autism, he says.

Opening the Drug Pipeline

All advocacy groups want a cure, or at least a treatment without grueling side effects. The 1983 Orphan Drug Act was supposed to promote such breakthroughs by offering tax reductions and extended patent protection for companies that created drugs to treat rare diseases. But development costs are still formidable. And companies that decide to take the risk can run into other obstacles, including a scarcity of patients for clinical trials. One of the main ways that advocacy groups have contributed is by working to remove some of these barriers.

For example, when it comes to new treatments, Kathy Giusti has delivered. The former executive at the pharmaceutical company G.D. Searle helped to start the Multiple Myeloma Research Foundation (MMRF) 8 years ago, after learning she had the incurable blood cancer. Although there are

about 16,000 new cases of multiple myeloma in the U.S. each year, it had drawn little interest from pharmaceutical companies, and at the time she was diagnosed the drug development pipeline was empty. One consequence of the more than $60 million the MMRF has collected for research is that the pipeline is flowing again, with three medications—Thalomid, Velcade, and Revlimid—recently approved for use against multiple myeloma. However, the MMRF's contribution goes beyond money. Research on the new drugs could have stalled without the organization's ability to reach patients. To ensure that clinical trials for all three drugs would not falter because of insufficient volunteers, the MMRF alerted patients through the clinical trials register of its web site, enrolling sufficient participants to allow the trials to proceed.

Progress on new epilepsy drugs halts long before the clinical trials stage, according to Warren Lammert, cofounder of the Epilepsy Therapy Development Project. The "kink in the therapy pipeline" is academic scientists, says Lammert. "There are many, many researchers with interesting and exciting ideas who don't know how to move them along to get therapeutics to patients." To address this shortcoming, the Epilepsy Therapy Development Project matches academics who have made an encouraging discovery with companies that have the expertise to commercialize it. Last year, for example, the organization brokered a deal to provide backing for Meir Bialer of Hebrew University of Jerusalem in Israel, who is seeking gentler derivatives of the standard epilepsy treatment valproic acid. Although the drug quells seizures, it can cause liver damage and trigger birth defects. Bialer had identified some promising alternatives, says Lammert, but was unable to raise the money for further investigation. So, the Project and Jazz Pharmaceuticals of Palo Alto, California agreed to split the development costs, with the company retaining the licensing rights. This matchmaking strategy hasn't yet put any drugs into the clinic, Lammert says, and its success will depend on a steady flow of new research findings.

A radical strategy for kick-starting drug research comes from James Heywood of the ALS Therapy Development Foundation, based in Cambridge, Massachusetts. Heywood launched the nonprofit drug-testing laboratory after his brother was diagnosed with ALS in 1998. What deters companies from working on diseases like ALS is not the small market for medications, Heywood says. It's the lack of drug targets with enough scientific support to justify the financial risk. In effect, people are saying to the industry, "We want you to develop drugs that we don't know will work." Academic research cannot provide the supporting evidence, he says. "Science tends to be a craft industry. You have experiments that are beautiful projects," but they can't furnish the quantity of information needed to choose whether to pursue a particular drug target. By taking over early drug testing, Heywood hopes to slash the cost of making this decision.

Making Connections

"One thing that the activist community has been good at is getting scientists to talk to each other," says Lerner. To engineer conversation and cooperation, some groups have established formal collaborations. An example is Giusti's latest effort, the Multiple Myeloma Research Consortium (MMRC), which unites experts at 11 of the top cancer centers in North America. Participants include the Mayo Clinic, the Dana-Farber Cancer Institute in Boston, and the University of Chicago. "It's not that people don't want to collaborate, it's that they are incredibly busy," says Giusti. Now, time-strapped myeloma researchers at these institutions have the chance to join projects such as a clinical trial of the experimental drug TKI 258, which blocks aberrant expression of the fibroblast growth factor receptor FGFR3 resulting from a translocation between chromosomes 4 and 14 in some multiple myeloma patients.

The Epilepsy Therapy Development Project has launched a similar consortium. Its united front benefits drug companies that want to start clinical trials, says Lammert. Instead of negotiating with the institutional review boards at every participating institution, a company only needs to deal with one.

But informal arrangements can also be productive, says Wexler. The Hereditary Disease Foundation has long sponsored unconventional workshops on Huntington's disease and related disorders. The rules ban slides—they discourage interaction, says Wexler—and require participants to discuss unpublished data and to dream up radical research strategies. One seemingly outrageous proposal from a 1979 workshop involved locating a marker for the Huntington's disease gene, something many researchers at the time thought would require 100 years, Wexler says. But after the participants concluded that the task was feasible, it took only 4 years. The discovery paved the way for identification of the Huntington's disease gene 9 years later.

Advocacy groups serve another crucial function, says Wexler. They link scientists to patients who suffer from the disease, allowing researchers to understand why they have been putting in long hours. At the Hereditary Disease Foundation workshops, she always makes sure that researchers talk with Huntington's disease patients and their families, so they can grasp that the illness "wasn't just theoretical." Gordon has followed suit in her HGPS meetings. For researchers who spend most of their time manipulating molecules in the lab, "that dialogue is incredibly motivating," says Michaelis.

Banking on the Future

Rarity makes a disease harder to study. For example, even obtaining one blood sample from an HGPS patient entails a logistical feat, given that only 12 children with the disease live in the U.S. today. Another way that advocacy groups are promoting research is by setting up the cell and tissue collections that are invaluable for probing disease mechanisms and for preliminary drug studies.

Cancer experts are already requesting samples from the new MMRC tissue bank housed at the Mayo Clinic Arizona in Scottsdale, says director Rafael Fonseca. It holds bone marrow and blood from some 800 patients provided by the 11 MMRC centers. Collection and storage of the material follows a standard protocol, and patients' clinical data are included. Those features make the bank an advance over previous scattered attempts to collect myeloma patient tissue, says Fonseca. Gordon considers the HGPS tissue bank, which opened in 2002 and contains cell lines derived from 54 patients, one of her most important contributions. It proved vital for recent discoveries about the disease because researchers used the material to track down the genetic defect underpinning HGPS and to conduct some of the preclinical studies of FTIs.

Another boon for gene hunters is CAN's tissue bank, the Autism Genetic Resource Exchange (AGRE). It houses donations from more than 800 families, each with at least two autistic children. Geschwind and his colleagues relied on AGRE samples to tease out candidate autism genes on chromosome 7. Rudy Tanzi of Harvard Medical School heads a bigger search using AGRE samples and new Affymetrix microarrays to evaluate 500,000 single nucleotide polymorphisms (SNPs). The group is conducting the first "unbiased screen of the whole genome" for autism susceptibility genes, says Tanzi. That strategy might uncover genes that no one suspected were involved in the disorder, he says. The researchers have already begun the analysis, and Tanzi says he expects the data to be ready by the end of the year.

Causes for Concern?

The new hands-on advocacy has paid off for many patients and researchers. But some scientists see drawbacks to this type of entrepreneurial approach. For example, Wexler says that the impatience of some groups to find cures can obstruct progress instead of fostering it. They sometimes opt for short-term projects and overlook the long-term research necessary to understand the disease. Moreover, in the free-for-all to attract donations and the interest of researchers, nobody sets priorities. The most successful advocacy groups don't necessarily represent the most prevalent diseases, and organizations lacking leaders with the energy of Gordon or the insider know-how of Giusti may not be as effective. Despite these limitations, scientists agree that activism by patients and their families can keep the hunt for new treatments for rare and neglected diseases moving forward.

Mitchell Leslie
Portland, Oregon
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